



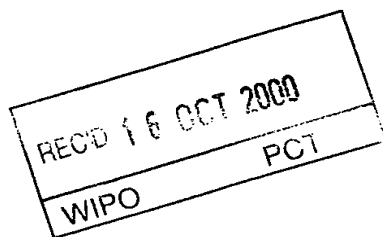
PCT/GB 00/03770



INVESTOR IN PEOPLE

68 00 / 3770

4



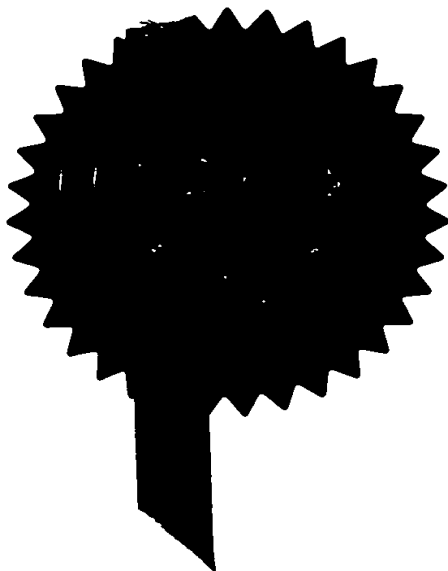
The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

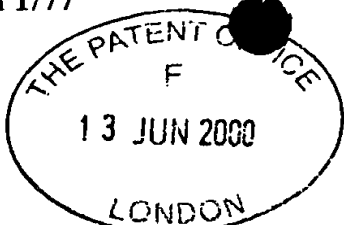
Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.



Signed

Dated 6 October 2000

THIS PAGE BLANK (USPTO)



The
**Patent
Office**

14JUN00 E544738-1 D00192
P01/7700 0.00-0014420.4

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form))

The Patent Office

Cardiff Road
Newport
Gwent NP10 8QQ

1. Your reference

P75428B

2. Patent application number

(The Patent Office will fill in this part)

0014420.4

13 JUN 2000

3. Full name, address and postcode of the or of each applicant (underline all surnames)

John CARTER
246 Kenton Road
Harrow
Middlesex HA3 8BY
United Kingdom

Patents ADP number (if you know it)

6643068001

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention

PHARMACEUTICAL COMPOSITIONS AND THEIR USE

5. Name of your agent (if you have one)

J A KEMP & CO

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

14 SOUTH SQUARE
GRAY'S INN
LONDON WC1R 5LX

Patents ADP number (if you know it)

26001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number

Country

Priority application number
(if you know it)

Date of filing
(day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing
(day / month / year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer "Yes" if:

NO

- a) any applicant named in part 3 is not an inventor, or
 - b) there is an inventor who is not named as an applicant, or
 - c) any named applicant is a corporate body:
- See note (d))

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form.
Do not count copies of the same document

Continuation sheets of this form NONE

Description 20

Claim(s) 3

Abstract 1

Drawing(s) 5 + 5

10. If you are also filing any of the following, state how many against each item.

Priority documents NONE

Translations of priority documents NONE

Statement of inventorship and right to grant of a patent (Patents Form 7/77) NONE

Request for preliminary examination and search (Patents Form 9/77) NONE

Request for substantive examination (Patents Form 10/77) NONE

Any other documents (please specify) NONE

11. I/We request the grant of a patent on the basis of this application

Signature

T. A. Koy 1/6

Date 13.06.00

12. Name and daytime telephone number of person to contact in the United Kingdom R.C. SRINIVASAN
020 7405 3292

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

- If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.
- Write your answers in capital letters using black ink or you may type them.
- If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.
- If you have answered "Yes" Patents Form 7/77 will need to be filed.
- Once you have filled in the form you must remember to sign and date it.
- For details of the fee and ways to pay please contact the Patent Office.

PHARMACEUTICAL COMPOSITIONS AND THEIR USE

This invention relates to pharmaceutical compositions and their use in the treatment of neoplastic disease.

There has long been a demand for a safe and effective treatment of neoplastic
5 disease. WO 84/04922 proposes the use of copper salicylate complexes for this purpose. However, the copper salicylate complexes of WO 84/04922 are not sufficiently effective to be put to widespread use.

It has now unexpectedly been discovered that a composition comprising an assimilable copper compound, a source of salicylic acid or a derivative thereof and
10 vitamin C, is particularly effective in the treatment of neoplastic disease.

The present invention therefore provides a composition comprising:

- (a) a physiologically acceptable source of assimilable copper;
- (b) a source of salicylic acid or a physiologically acceptable derivative thereof; and
- 15 (c) vitamin C.

Addition of vitamin C to components (a) and (b) leads to a synergistic increase in effectiveness.

Preferably, the composition of the invention further comprises (d), a physiologically acceptable source of assimilable manganese. Alternatively, the
20 composition of the invention may further comprise (e), a physiologically acceptable source of assimilable iron or (f), a physiologically acceptable source of assimilable sulfur. Compositions of the invention comprising both (e) and (f) are particularly preferred.

Particularly preferred compositions of the invention are those comprising:

- 25 (a) a physiologically acceptable source of assimilable copper;
- (b) a source of salicylic acid or a physiologically acceptable derivative thereof;
- (c) vitamin C;
- (d) a physiologically acceptable source of assimilable manganese;
- 30 (e) a physiologically acceptable source of assimilable iron; and
- (f) a physiologically acceptable source of assimilable sulfur.

It has also unexpectedly been found that compositions of the invention further comprising a physiologically acceptable source of assimilable zinc are particularly effective in the treatment of sarcomas.

The present invention therefore also provides a composition of the invention,
5 further comprising a physiologically acceptable source of assimilable zinc.

The sources of copper, manganese, iron and zinc used in the composition of the present invention preferably contain the metals in ionic form, e.g. as salts with organic or inorganic acids. However, other metal compounds which provide assimilable forms of the metals, e.g. metal oxides, can also be used.

10 Thus, a physiologically acceptable source of assimilable copper is typically a copper oxide or a salt of copper with an organic or inorganic acid. A physiologically acceptable source of assimilable manganese is typically a manganese oxide or a salt of manganese with an organic or inorganic acid. A physiologically acceptable source of assimilable iron is typically an iron oxide or a salt of iron with an organic
15 or inorganic acid. A physiologically acceptable source of assimilable zinc is typically a zinc oxide or a salt of zinc with an organic or inorganic acid.

Suitable physiologically acceptable salts of the above metals with organic acids include salts with orotic acid, aspartic acid, gluconic acid, tartaric acid, citric acid, lactic acid, acetic acid, fumaric acid, maleic acid, malic acid, ascorbic acid,
20 succinic acid, benzoic acid, methanesulphonic acid, ethanesulphonic acid, benzenesulphonic acid and p-toluenesulphonic acid. Suitable physiologically acceptable salts of the above metals with inorganic acids include salts with hydrochloric acid, hydrobromic acid, hydriodic acid, phosphoric acid, diphosphoric acid, nitric acid or sulfuric acid, preferably hydrochloric, hydrobromic, hydriodic,
25 phosphoric or sulfuric acid. Such salts are available commercially or may be prepared if desired by known methods.

Preferred physiologically acceptable salts are salts with organic acids, more preferably salts with orotic acid, aspartic acid, gluconic acid, tartaric acid, citric acid, lactic acid or acetic acid and most preferred are salts with orotic or gluconic acid.

30 It is also preferred that the physiologically acceptable salts are water soluble, for example salts with gluconic acid.

It is particularly preferred that the physiologically acceptable salt of assimilable copper is copper orotate or copper gluconate, most preferably copper gluconate. It is particularly preferred that the physiologically acceptable salt of assimilable manganese is manganese orotate or manganese gluconate, most

5 preferably manganese gluconate. It is particularly preferred that the physiologically acceptable salt of assimilable iron is iron orotate or iron gluconate, most preferably iron gluconate. It is particularly preferred that the physiologically acceptable salt of assimilable zinc is zinc orotate or zinc gluconate, most preferably zinc gluconate.

When, as is preferred, the compound of the invention contain more than
10 one metal, all the metal salts preferably include the same anion. This anion is typically orotate or gluconate, preferably gluconate.

The source of salicylic acid or a physiologically acceptable derivative thereof is typically salicylic acid or a physiologically acceptable derivative thereof. Typically, the said derivative is a compound in which the carboxyl or hydroxyl
15 function of salicylic acid has been converted into a derivative.

A physiologically acceptable derivative of salicylic acid is typically a salicylic acid metal salt, ester or amide. Examples of suitable metal salts include alkali metal salts, for example sodium and potassium salts, and alkaline earth metal salts, for example calcium and magnesium salts. Sodium salicylate is most
20 preferable.

Examples of suitable esters include C_{1-6} alkyl esters, for example methyl, ethyl, propyl, butyl, pentyl or hexyl esters and particularly preferred are the methyl and ethyl esters. Examples of suitable amides are amides obtainable by reacting salicylic acid with an amine HNR_1R_2 , wherein R_1 and R_2 may be the same or
25 different and are selected from hydrogen and C_{1-6} alkyl groups such as methyl, ethyl, propyl, butyl, pentyl or hexyl. R_1 and R_2 are preferably selected from hydrogen, methyl and ethyl and most preferably both R_1 and R_2 are hydrogen.

Derivatives in which both the hydroxyl function and the carboxyl function of salicylic acid have been converted into a derivative can also be used.

30 When the hydroxyl function of salicylic acid is converted to a derivative it is typically converted to an ester, for example a C_1-C_6 alkyl ester such as acetyl-

salicylic acid (aspirin).

A particularly preferred derivative of salicylic acid is sodium salicylate.

Salicylic acid itself and suitable derivatives of it are commercially available.

Components (a) and (b) may be present in the composition of the invention as
5 a copper salicylate complex. As used herein, a copper salicylate complex is a
complex of copper and salicylic acid or a complex of copper and a said
physiologically acceptable derivative of salicylic acid.

Typically, the physiologically acceptable source of assimilable sulfur is
elemental sulfur and any allotropic form of sulfur may be used. Preferably, sulfur is
10 present in the composition in the form of sublimed sulfur or precipitated sulfur, most
preferably sublimed sulfur.

The compositions of the invention typically comprise 15 to 60, preferably 25
to 40, parts by weight copper gluconate, or equivalent amount of active ingredient
when a physiologically acceptable source of assimilable copper other than copper
15 gluconate is used.

Typically, the compositions of the invention comprise from 300 to 600,
preferably 300 to 400, most preferably 350, parts by weight sodium salicylate, or
equivalent amount of active ingredient when salicylic acid or a physiologically
acceptable derivative thereof other than sodium salicylate is used.

20 Typically, the compositions of the invention comprise from 200 to 1000,
preferably 300 to 500, most preferably 400, parts by weight vitamin C. Preferably,
vitamin C is present in the compositions of the invention in an amount significantly
larger than that which is regarded as the normal minimum daily requirement for an
adult.

25 Typically, the compositions of the invention containing a physiologically
acceptable source of assimilable manganese, comprise from 15 to 60, preferably 25
to 40, parts by weight manganese gluconate, or equivalent amount of active
ingredient when a physiologically acceptable source of assimilable manganese other
than manganese gluconate is used.

30 Typically, the compositions of the invention containing a physiologically
acceptable source of assimilable iron, comprise from 15 to 60, preferably 25 to 40,

parts by weight iron gluconate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable iron other than iron gluconate is used.

Typically, the compositions of the invention containing a physiologically acceptable source of assimilable sulfur, comprise from 15 to 60, preferably 25 to 40, parts by weight sulfur.

Typically, the compositions of the invention containing a physiologically acceptable source of assimilable zinc, comprise from 15 to 60, preferably 25 to 40, parts by weight zinc gluconate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable zinc other than zinc gluconate is used.

The parts by weight referred to are based on the total weight of these ingredients in the composition.

The amounts of the active ingredients in the compositions of the invention should be calculated having regard to the intended dosage to be administered. When the composition is to be administered orally, as is usual, a suitable dosage is about 2ml volume for each 60 lbs of body weight of the subject to be treated. This dosage can be administered up to three times a day. The 2ml volume dosage typically contains from 8 to 35 mg, preferably from 14 to 25 mg of copper gluconate, or an equivalent amount of active ingredient when a physiologically acceptable source of copper other than copper gluconate is used. The 2ml volume dosage typically contains from 170 to 350 mg, preferably from 170 to 230 mg and most preferably about 200 mg sodium salicylate or an equivalent amount of active ingredient when salicylic acid or a physiologically acceptable derivative thereof other than sodium salicylate is used. The 2ml volume dosage typically contains from 110 to 570 mg, preferably from 170 to 285 mg and most preferably about 230 mg vitamin C.

A suitable dosage of about 2 ml volume of the compositions of the invention comprising a physiologically acceptable source of assimilable manganese, typically contains from 8 to 35 mg, preferably from 14 to 25 mg of manganese gluconate or an equivalent amount of active ingredient when a physiologically acceptable source of manganese other than manganese gluconate is used.

A suitable dosage of about 2 ml volume of the compositions of the invention comprising a physiologically acceptable source of assimilable iron typically contains from 8 to 35 mg, preferably from 14 to 25 mg of iron gluconate or an equivalent amount of active ingredient when a physiologically acceptable source of iron other
5 than iron gluconate is used.

A suitable dosage of about 2ml volume of the compositions of the invention comprising a physiologically acceptable source of assimilable sulfur typically contains from 8 to 35 mg, preferably from 14 to 25 mg of sulfur.

1 A suitable dosage of about 2 ml volume of the compositions of the invention
10 comprising a physiologically acceptable source of assimilable zinc typically contains from 8 to 35 mg, preferably from 14 to 25 mg of zinc gluconate or an equivalent amount of active ingredient when a source of zinc other than zinc gluconate is used.

These figures are approximate and considerable variation in the proportions of the active ingredients is possible without losing the valuable properties of the
15 compositions.

The compositions of the invention may be made by first forming an intimate mixture of the metals to be used in the form of suitable salts or other derivatives, together with sulfur, if present. This mixture in finely ground form can then be added to an aqueous solution or suspension of the salicylic acid or derivative thereof.
20 Typically, from 2 to 5 ml, preferably about 3½ ml of aqueous solution or suspension is used. This solution preferably contains 5-20%, preferably about 10%, by weight of salicylic acid or derivative. The vitamin C may be added before or after the salicylic acid solution, and is preferably added before the salicylic acid solution such that all of the solid ingredients are combined first. The resulting slurry or solution
25 may be administered orally.

The compositions of the invention are thought to work by promoting the formation of the enzyme superoxide dismutase (SOD). SOD functions as a free radical scavenger and reduces DNA damage caused by free radical attack.

The compositions of the invention may be used in human and veterinary
30 medicine, for example in the treatment of cats and dogs. They are useful in the treatment or prevention of a neoplastic disease. They are capable of improving the

condition of a patient suffering from a cancer.

Typically, a human or animal is treated by initially administering said dosage of 2 ml of the composition of the invention, comprising active ingredients in the amounts set out above, in the form of an aqueous solution or suspension, per 60 lbs
5 body weight of subject followed by a half dose of a similar solution or suspension 1 to 2 hours later. Four hours later a further half dose may be given. Subsequent treatment (when the tumour has noticeably regressed and/or the symptoms have been considerably alleviated) may consist of the oral administration of 2 ml of the said solution or suspension per 60 lbs body weight of subject once a day. This may be
10 given for three weeks, then, if further progress has been made, the dose may be reduced to 2 ml per 60 lbs body weight on alternate days for 3 weeks. The frequency of dosing may be further reduced as further progress is made.

The compositions of the invention have been found effective in treatment of carcinomas of the breast, rectum, bladder, liver, peritoneum, stomach and urethra,
15 and in some lymphomas. Compositions of the invention comprising a physiologically acceptable source of assimilable zinc are effective against sarcomas. The treatment may be continued until there is a marked regression in the size of the tumour or until the tumour disappears.

The compositions of the invention are normally administered orally.
20 Preferably, therefore they are suitable for oral administration. Suitable forms for oral administration include, for example, tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules. Preferred forms for oral administration are tablets and capsules. However, other routes of administration may be possible provided suitable precautions are taken to make the compositions
25 suitable for administration in the contemplated way. For example, the compositions of the invention may be administered parenterally, whether subcutaneously, intravenously, intramuscularly, intrasternally, transdermally or by infusion techniques, or as a suppository.

It has been found that the effectiveness of the compositions of the invention
30 can be enhanced if they are administered in conjunction with a dietary regime which is low in salt and high in potassium and essential amino acids such as proline, serine,

glutamine, lysine, histidine, alanine, methionine and leucine. By way of example, vegetables and fruit may be mentioned as foods which have high potassium content. Porridge oats, for example, have a high potassium, low salt content. By way of example, liver may be mentioned as a food source rich in essential amino acids.

- 5 Typically, for a human patient about 2 oz of liver per day has been found to be sufficient.

It has been found also that better results are obtained by supplementing the diet of a subject with additional vitamin C, i.e. vitamin C in addition to that preferably contained in the compositions of the invention. For example, the

- 10 administration of 1 g of vitamin C per 20 lbs subject body weight per day, has been found to enhance the activity of the new compositions. Likewise, administration of nicotinic acid, for example 25 mg per 14 lbs subject body weight per day, has been found to give rise to improved activity of the compositions of the invention.

The following Examples illustrate the invention.

EXAMPLE 1

Copper (II) orotate (35 mg) and manganese (II) orotate (35 mg), in finely divided form were mixed dry. Sodium salicylate solution (3.5 ml of a 10% aqueous solution) was then added followed by vitamin C (400 mg). The resulting suspension is suitable for immediate oral administration.

EXAMPLE 2

Copper (II) orotate (35 mg), manganese (II) orotate (35 mg) and zinc orotate (35 mg) in finely divided form were mixed dry. 3.5 ml of a 10% aqueous solution of sodium salicylate (i.e. 3.5 ml of an aqueous solution containing 350 mg sodium salicylate) was then added followed by vitamin C (400 mg). The resulting suspension is suitable for immediate oral administration.

EXAMPLE 3

To copper (II) orotate (35 mg) in finely divided form was added sodium salicylate solution (3.5 ml of a 10% aqueous solution) followed by vitamin C (400 mg). The resulting suspension is suitable for immediate oral administration.

EXAMPLE 4

Copper (II) orotate (35 mg), manganese (II) orotate (35 mg), iron (II) orotate (35 mg) and sublimed sulfur (35 mg), in finely divided form were mixed dry. Sodium salicylate solution (3.5 ml of a 10% aqueous solution) was then added followed by vitamin C (400 mg). The resulting suspension is suitable for immediate oral administration.

EXAMPLE 5

Copper (II) orotate (35 mg), manganese (II) orotate (35 mg), iron (II) orotate (35mg), sublimed sulfur (35mg) and zinc orotate (35 mg) in finely divided form were mixed dry. 3.5 ml of a 10% aqueous solution of sodium salicylate (i.e. 3.5 ml of an aqueous solution containing 350 mg sodium salicylate) was then added

followed by vitamin C (400 mg). The resulting suspension is suitable for immediate oral administration.

EXAMPLE 6

Copper (II) gluconate (35 mg), vitamin C (400 mg) and manganese (II) gluconate (35 mg), in finely divided form were mixed dry. Sodium salicylate solution (3.5 ml of a 10% aqueous solution) was then added. The resulting solution is suitable for immediate oral administration.

EXAMPLE 7

Copper (II) gluconate (35 mg), vitamin C (400 mg), manganese (II) gluconate (35 mg) and zinc gluconate (35 mg) in finely divided form were mixed dry. 3.5 ml of a 10% aqueous solution of sodium salicylate (i.e. 3.5 ml of an aqueous solution containing 350 mg sodium salicylate) was then added. The resulting solution is suitable for immediate oral administration.

EXAMPLE 8

To copper (II) gluconate (35 mg) and vitamin C (400 mg) in finely divided form was added sodium salicylate solution (3.5 ml of a 10% aqueous solution). The resulting solution is suitable for immediate oral administration.

EXAMPLE 9

Copper (II) gluconate (35 mg), vitamin C (400 mg), manganese (II) gluconate (35 mg), iron (II) gluconate (35 mg) and sublimed sulfur (35 mg), in finely divided form were mixed dry. Sodium salicylate solution (3.5 ml of a 10% aqueous solution) was then added. The resulting suspension is suitable for immediate oral administration.

EXAMPLE 10

Copper (II) gluconate (35 mg), vitamin C (400 mg), manganese (II) gluconate (35 mg), iron (II) gluconate (35mg), sublimed sulfur (35mg) and zinc gluconate (35 mg) in finely divided form were mixed dry. 3.5 ml of a 10% aqueous solution of

sodium salicylate (i.e. 3.5 ml of an aqueous solution containing 350 mg sodium salicylate) was then added. The resulting suspension is suitable for immediate oral administration.

5

EXAMPLE 11

This experiment was conducted at University College London under Home Office License. In this experiment 100 C57B1 male mice were injected subcutaneously with a transplantable RMA thymoma tumour. 50 of the mice were used as controls and 50 mice were experimental mice.

10

Mice have a much faster rate of metabolism than larger mammals. It was therefore decided to give the mice a larger dose of the formula than the dose which would be suitable for larger animals such as cats and dogs. This latter dose was accordingly increased by a factor of 10.

15

For a 30 g mouse, 0.022 ml of the solution prepared in Example 1 was administered. This was administered to the mice three times a day at 10 am, 3 pm and 6 pm. The composition was administered by gavage. In addition the experimental mice were fed on a diet of organic wheat, barley, oats and rye.

The general condition of the experimental and control mice following tumour injection is shown in Table 1.

20

Table 1

RMA thymoma in C57B1 male mice		
Days after Tumour injection	Control	Experimental
16	All mice have tumours. 2 killed because of large tumour size.	20/22 with palpable tumours. 2 probably have deep tumours. 1 sick mouse killed.
18		3 mice died as a result of treatment. 2 with small tumours. 1 had only a large lymph node.
20	4 mice killed with large tumours.	2 sick mice killed, both had tumours.
21	Remaining mice killed because of large tumours. All tumours firm and infiltrating muscle of thigh or peritoneal wall.	4 killed with large infiltrating tumours.
23		3/12 mice had superficial freely mobile plaque like tumours.
25		6 mice killed because of large tumour size. All tumours firm and infiltrating. 1 mouse had an axillary abscess.
29		4/6 remaining tumours fixed. Large lymph nodes palpable.
31		Remaining mice killed. 5/6 tumours infiltrating deeply. 1/6 more superficial but draining node grossly enlarged.

The growth of the tumour in experimental and control mice is shown in Figure 1. The weights of the experimental and control mice are shown in Figure 2.

The growth of the thymoma tumour was measured by callipers, i.e. the diameter of the surface of the tumour was determined. The tumours were not

weighed at the end of the experiment.

As can be seen from Figure 1, 21 days after tumour injection the tumours in the control mice were approximately 1.9 times larger than those in the experimental mice.

- 5 Apart from deaths caused by the stress of gavage, to which the control mice were not subjected, the only side effect observed was slight weight loss, probably attributable to the change of diet.

EXAMPLE 12

- 10 This experiment was conducted at University College London under Home Office License. Transplantable mammary carcinomas were injected into 100 male Balb/c mice. 50 of the mice were used as controls and 50 mice were experimental mice.

- 15 These tumours grew much more slowly than the thymomas injected in Example 11. Accordingly, less treatment was given to the experimental mice; they were gavaged only once a day with 0.22 ml of the solution prepared in Example 1 and fed on a diet of organic grains as described in Example 11. Nevertheless a result was obtained as can be seen from Figure 3 showing the growth of the mammary carcinoma in experimental and control mice. But because they were given less
20 treatment the difference in growth rate between the experimental and control group is much less than that observed in Example 11.

- 25 The tumours in the control group were only 1.14 times larger than in the experimental group at 23 days after tumour injection. However, 29 days after tumour injection the tumours in the control group were 1.19 times larger than the tumours in the experimental group.

Apart from deaths caused by the stress of gavage, to which the control mice were not subjected, the only side effect observed was slight weight loss, probably attributable to the change of diet.

EXAMPLE 13

Professor Peter Beverley of the Department of Oncology at University College London Medical School stated that although there was a statistically higher significant effect in tumour growth between the experimental and control mice in
5 Examples 11 and 12, it was clear that the treatment by repeated gavage was stressful so that untreated mice were not a perfect control.

It was therefore decided that a further experiment should be performed but that this time the formula should be administered in the drinking water and given to the mice by gavage only once a day. As a water soluble copper salt was required for
10 addition to the drinking water, it was decided to use copper gluconate in place of copper orotate. The control mice would also have the same organic grains diet as the experimental mice and be gavaged with water once a day. It was also decided that the experimental mice should be given extra vitamin C by having the vitamin C added to their drinking water.

15 This experiment was conducted at University College London under Home Office License.

Copper (II) gluconate, 35 mg, and manganese (II) orotate, 35 mg, in finely divided form were mixed dry. Sodium salicylate solution (3.5 ml of a 10% aqueous solution) was then added followed by vitamin C (400 mg).

20 The vitamin C was added to the drinking water of the experimental mice by putting 300 mg of vitamin C in 50 ml of water three times a day. Thus each cc contained 6 mg vitamin C. Each mouse drank on average 4 ml of water containing 24 mg of vitamin C three times a day. So each mouse received on average 72 mg of vitamin C per day.

25 50 C57B1 male mice were injected subcutaneously with a transplantable thymoma. 24 mice, the experimental mice, were treated, and 26 mice were used as a control.

It was decided to give the mice a larger dose of the formula because they would be gavaged only once a day and it was not sure how much drinking water each
30 mouse would drink.

The dose per mouse compared to larger mammals was now increased by a

factor of 17.

Each mouse was gavaged with 0.04 ml of the composition prepared above once a day.

0.5 ml of the composition prepared above was added to the drinking water three times a day. 50 ml of drinking water was provided three times a day. 0.5 ml in 50 ml is 0.01 ml per cc. Each mouse drank approximately 4 ml of water three times a day so each mouse received approximately 0.04 ml of the composition in their drinking water three times a day. Each mouse therefore received approximately a total of $0.04 \times 3 = 0.12$ ml of the composition from the drinking water each day plus 10 0.04 ml from the gavage, a total of 0.16 ml per day.

During the trial 4 mice from the experimental group and 5 from the control group died because of the gavage. The mice were all killed on day 17 and the tumours were dissected out and weighed. However, two tumours from the control group could not be removed for measurement because they were too extensive. The 15 results are shown in Table 2.

Table 2

EXPERIMENTAL GROUP		CONTROL GROUP	
Mouse No.	Tumour Weight (g)	Mouse No.	Tumour Weight (g)
5	1	20	.40
	2	21	.50
	3	22	.50
	4	23	.60
	5	24	.60
10	6	25	.90
	7	26	.90
	8	27	.90
	9	28	1.00
	10	29	1.00
15	11	30	1.00
	12	31	1.10
	13	32	1.10
	14	33	1.30
	15	34	1.30
20	16	35	1.30
	17	36	1.50
	18	37	1.70
	19	38	1.80
25	Average tumour weight	39	1.80
		Average tumour weight	1.1

It can be seen from Table 2 that the combined weight of tumours from the experimental group was 9.1 grams. The combined weight of the tumours from the control group was 21.2 grams. The control group tumour mass was therefore $21.2/9.1 = 2.32$ times larger than the experimental group tumour mass.

5 Further, the average tumour weight in the control mice was 1.1 g. The average tumour weight in the experimental mice was 0.48g.

The average control group tumour mass is therefore $1.1/0.48 = 2.29$ times larger than the average experimental group tumour mass.

The difference in the size of the tumours as measured by callipers during the trial is shown in Figure 5. It can be seen from Figure 5 that by day 17 the difference in size between the control and experimental tumours, as measured by callipers, is $8.8/3.6 = 2.44$ times larger. Again there were no detectable side effects.

Professor Beverley has stated that this experiment has confirmed unequivocally that the treatment causes a statistically highly significant difference in tumour growth between the treated and control mice with no detectable side effects.

EXAMPLE 14

A 30lb 6 year old Manchester Terrier suffering from a spindle cell tumour was treated with the composition described in Example 1.

20 Before the treatment the animal had a hard lumpy swelling extending over the external side of the left foreleg from below the elbow joint up to the side of the shoulder. This diagnosis was made by Abbey Veterinary Clinics, London, who recommended amputation of the foreleg. 1cc of the composition was administered orally once a day for 5 days. By the end of 5 days the tumour had reduced in size considerably. The dose was then reduced to 1cc on alternate days for a further 7 days.

In addition, an extra 3 g vitamin C was administered orally every day and nicotinic acid was administered orally in an amount of 125mg per day.

A dietary regime was followed of organic fruits, organic vegetables, organic grains and lamb's liver to supply essential amino acids. Salt added to food was avoided.

Following the above treatment, the tumour disappeared. This result was certified by Mr. A. Sebesteny, head vet at the Imperial Cancer Research Fund, Clare Hall Laboratories.

5

EXAMPLE 15

A 60lb, 11 year old Doberman bitch was treated with a composition consisting of 30 mg copper orotate, 30 mg manganese orotate, 400 mg vitamin C and 3½ ml of an aqueous solution containing 350 mg sodium salicylate, prepared as in Example 1.

10

The animal was suffering from a urethral obstruction caused by an infiltrating malignant neoplasm thought to be a transitional cell carcinoma. This diagnosis was made at the department of Clinical Veterinary Medicine, Cambridge University. Before the treatment it could pass only a few drops of water with intense straining.

On the first day of treatment, the animal was given 2cc of the above
15 composition (administered orally). On the second day it was given 2cc, followed by 1cc an hour later, then ½cc an hour after that. This was repeated every day for a week, after which time an improvement was noted. The dosage was then reduced to 2cc once a day for a further 3 weeks.

In addition, an extra 6 g vitamin C was administered orally every day and
20 nicotinic acid was administered orally in an amount of 250 mg per day. A dietary regime as set out in Example 14 was followed.

Following the above treatment, the animal showed none of the former symptoms. It was still alive and in excellent health 4 years after the treatment, as can be confirmed by its owner.

25

EXAMPLE 16

An 80lb, 6 year old Alsatian was treated with a composition consisting of 50 mg copper orotate, 50 mg manganese orotate, 50 mg zinc orotate, 400 mg vitamin C and 3½ ml of an aqueous solution containing 350 mg sodium salicylate, prepared in
30 the same way as in Example 1, except that the zinc orotate was mixed dry in finely divided form together with the copper and manganese orotate.

The animal was suffering from a nasal tumour, thought to be a sarcoma and could not breathe through its nose. This diagnosis was made by the Department of Small Animal Medicine and Surgery, Royal Veterinary College, London. It had a large, hard, golf-ball sized swelling under the right eye.

5 It was given 2.6cc of the above composition, followed by 1.3cc an hour later (administered orally). This dose was repeated daily for 2 weeks by which time the tumour had significantly regressed, to the extent that the animal could breathe through its nose. The dosage was then reduced to alternate days for a fortnight, then to twice a week, then once a week.

10 In addition, an extra 8 g vitamin C was administered orally every day and nicotinic acid was administered orally in an amount of 330 mg per day.

A dietary regime as set out in Example 14 was followed.

By the end of the above treatment, the animal was symptom free. This result was certified by Mr. A. Sebesteny, head vet at the Imperial Cancer Research Fund.

15

EXAMPLE 17

A 60lb, 7 year old Doberman dog was treated with the composition described in Example 15. It was suffering from carcinoma of the peritoneum. This diagnosis was made by the Department of Small Animal Medicine and Surgery, Royal
20 Veterinary College, London. The animal was in an emaciated state, with a large swelling on the abdomen.

It was treated with 2cc of the composition, followed by 1cc an hour later (administered orally) every day for two weeks. After two weeks, the dosage was reduced to 2cc per day for a further two weeks, followed by a further reduction to
25 2cc on alternate days for another two weeks.

In addition, an extra 6 g vitamin C was administered orally each day and nicotinic acid was administered orally in an amount of 250 mg per day.

A dietary regime as set out in Example 14 was followed. After the above treatment the animal was symptom free, as can be confirmed by its owners.

30

EXAMPLE 18

A 150 lb human male around 45 years old, was treated with the composition described in Example 15. He was suffering from T-cell lymphoma, diagnosed at the Cromwell Hospital, London.

5 He was given 4.5cc of the composition (administered orally) once a day for 6 weeks (excluding Sundays). After this time, a regression was noted and the dosage was reduced to alternate days for 2 weeks, followed by a further reduction to once a week for three weeks.

In addition, an extra 15 g of vitamin C was administered orally every day and nicotinic acid was administered orally in an amount of 625 g per day.

10 A dietary regime as set out in Example 14 was followed. Following the above treatment, all symptoms disappeared. He is still alive and well 6 years after the treatment.

CLAIMS

1. A composition comprising:
 - (a) a physiologically acceptable source of assimilable copper;
 - 5 (b) a source of salicylic acid or a physiologically acceptable derivative thereof; and
 - (c) vitamin C.
2. A composition according to claim 1, further comprising (d) a physiologically acceptable source of assimilable manganese.
- 10 3. A composition according to claim 1 or 2, further comprising (e) a physiologically acceptable source of assimilable iron and (f) a physiologically acceptable source of assimilable sulfur.
4. A composition according to any one of the preceding claims, further comprising a physiologically acceptable source of assimilable zinc.
- 15 5. A composition according to any one of the preceding claims, wherein the said metals are present in the form of salts with organic or inorganic acids.
6. A composition according to any one of the preceding claims, in which components (a) and (b) are present as a copper salicylate complex.
7. A composition according to claim 5, wherein the salts are the same or
20 different and are selected from orotates, aspartates, gluconates, tartrates, citrates, lactates and acetates.
8. A composition according to claim 5 wherein the salts are the same or different and are selected from chlorides, bromides, iodides, phosphates and sulphates.
- 25 9. A composition according to any one of the preceding claims wherein the derivative of salicylic acid is sodium salicylate.
10. A composition according to any one of the preceding claims comprising:
 - (a) 15 to 60 parts by weight copper gluconate, or equivalent amount of
30 active ingredient when a physiologically acceptable source of assimilable copper other than copper gluconate is used;

(b) 300 to 600 parts by weight sodium salicylate, or equivalent amount of active ingredient when salicylic acid or a physiologically acceptable derivative thereof other than sodium salicylate is used; and

(c) 200 to 1000 parts by weight vitamin C.

5 the parts by weight referred to being based on the total weight of these ingredients in the composition.

11. A composition according to claim 10, further comprising 15 to 60 parts by weight manganese gluconate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable manganese other than
10 manganese gluconate is used.

12. A composition according to claim 10 or claim 11, further comprising 15 to 60 parts by weight of iron gluconate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable iron other than iron gluconate is used, and 15 to 60 parts by weight of sulfur.

13. A composition according to any one of claims 10 to 12, further comprising 15 to 60 parts by weight zinc gluconate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable zinc other than zinc gluconate is used.

14. A composition according to claim 10, comprising:

20 (a) 25 to 40 parts by weight copper gluconate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable copper other than copper gluconate is used;

(b) 350 parts by weight sodium salicylate, or equivalent amount of active ingredient when salicylic acid or a physiologically acceptable derivative thereof
25 other than sodium salicylate is used; and

(c) 400 parts by weight vitamin C.

the parts by weight referred to being based on the total weight of these ingredients in the composition.

15. A composition according to claim 14, further comprising 25 to 40
30 parts by weight manganese gluconate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable manganese other than

manganese gluconate is used.

16. A composition according to claim 14 or claim 15, further comprising 25 to 40 parts by weight of iron gluconate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable iron other than iron gluconate is used, and 25 to 40 parts by weight of sulfur.

17. A composition according to any one of claims 14 to 16, further comprising 25 to 40 parts by weight zinc gluconate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable zinc other than zinc gluconate is used.

18. A composition according to any one of the preceding claims for use in the treatment of the human or animal body.

19. Use of a composition according to any one of claims 1 to 17 in the manufacture of a medicament for use in the treatment or prevention of a neoplastic disease.

20. Products containing:

(a) a composition as claimed in any one of claims 1 to 17; and

(b) ~~vitamin C and/or one or more amino acids and/or nicotinic acid,~~

as a combined preparation for simultaneous, separate or sequential use in the treatment of neoplastic disease.

ABSTRACT

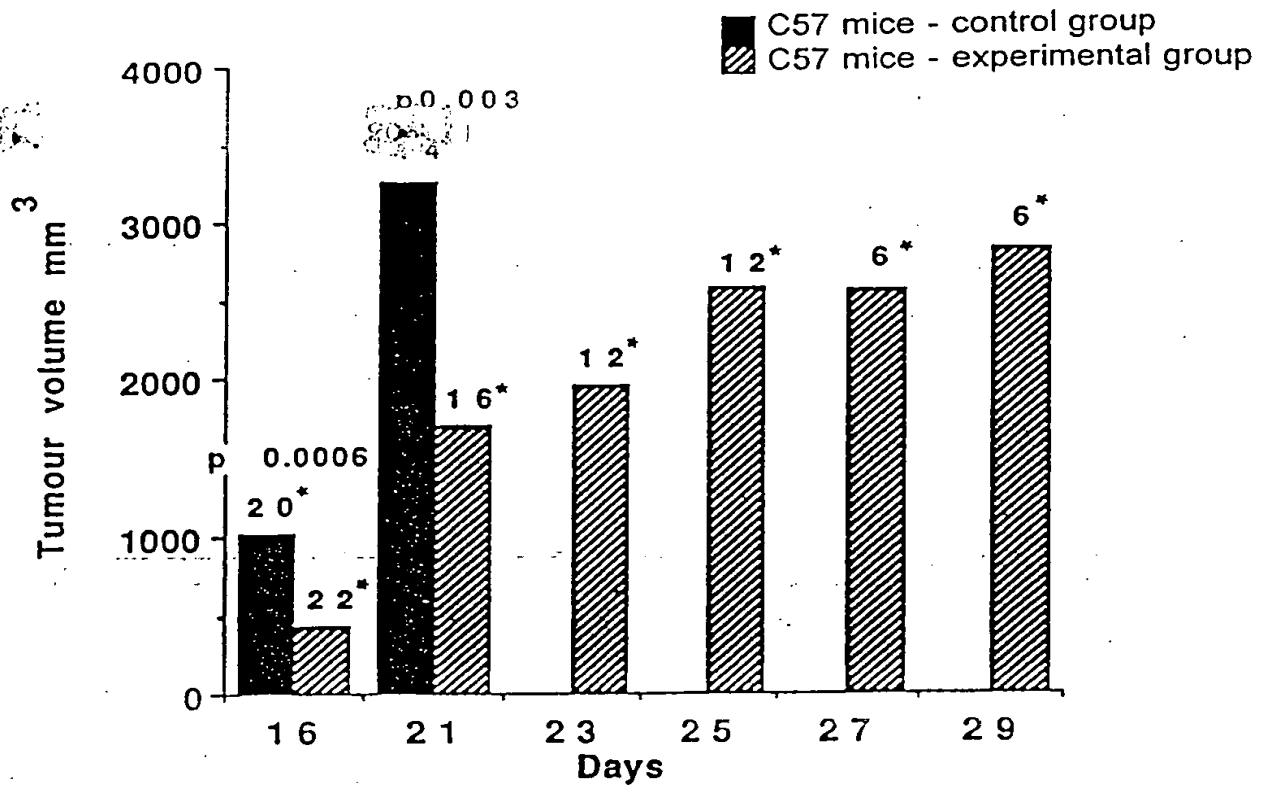
PHARMACEUTICAL COMPOSITIONS AND THEIR USE

A composition comprising:

- (a) a physiologically acceptable source of assimilable copper;
- 5 (b) a source of salicylic acid or a physiologically acceptable derivative thereof; and
- (c) vitamin C.

Figure 1. Growth of thymoma

Note that size of experimental tumours at late time points is artefactually small as those with the largest tumours have been killed

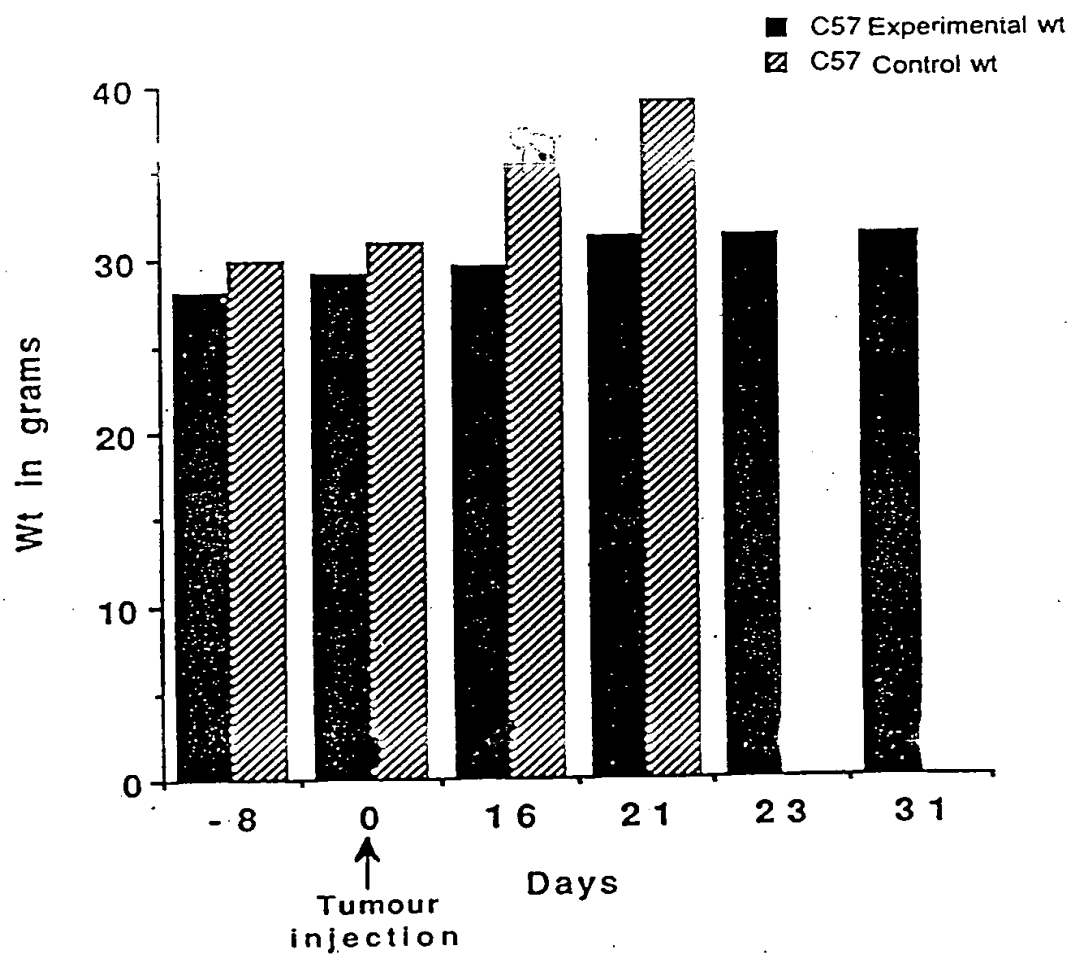


* No. of mice remaining

THIS PAGE BLANK (USPTO)

Figure 2

Weight of C57 mice

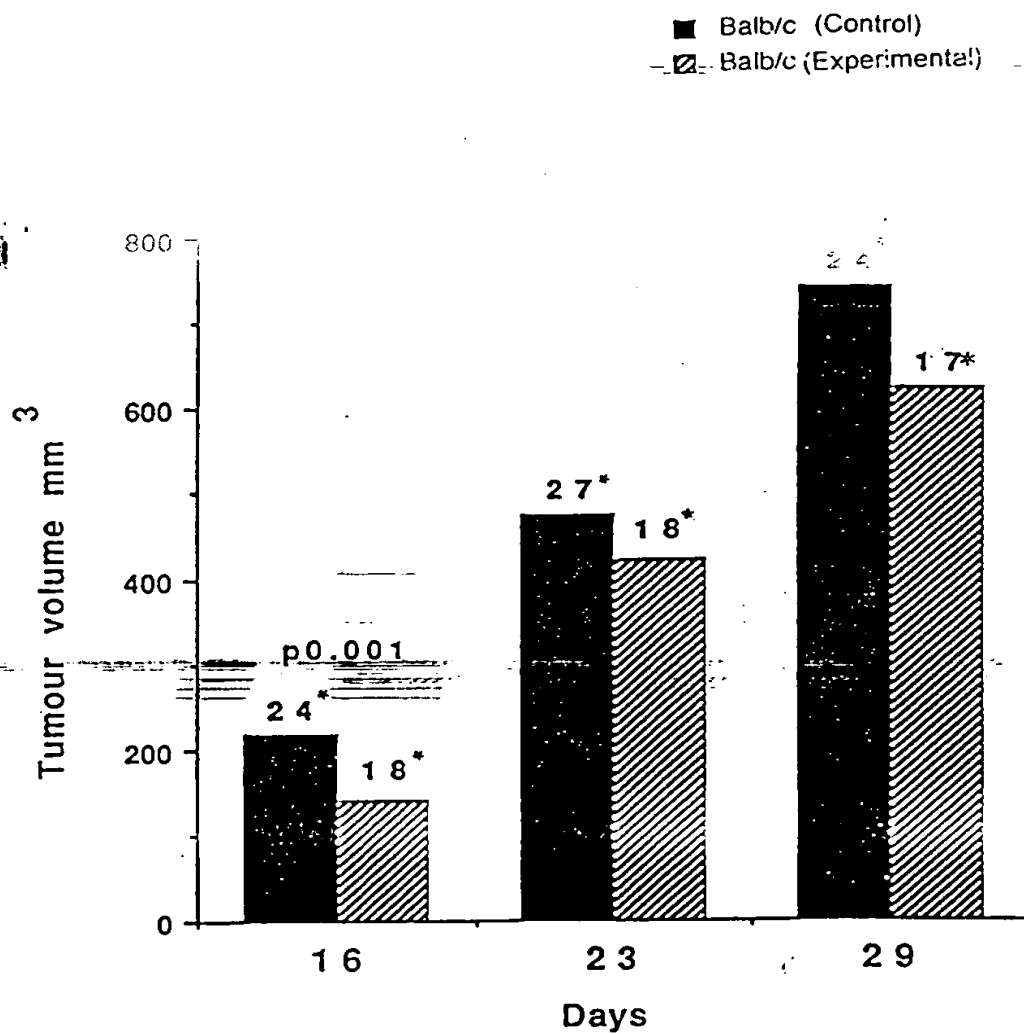


IS PAGE BLANK (USPTO)

11/15/11

11/15/11

Figure 3. Growth of mammary carcinoma

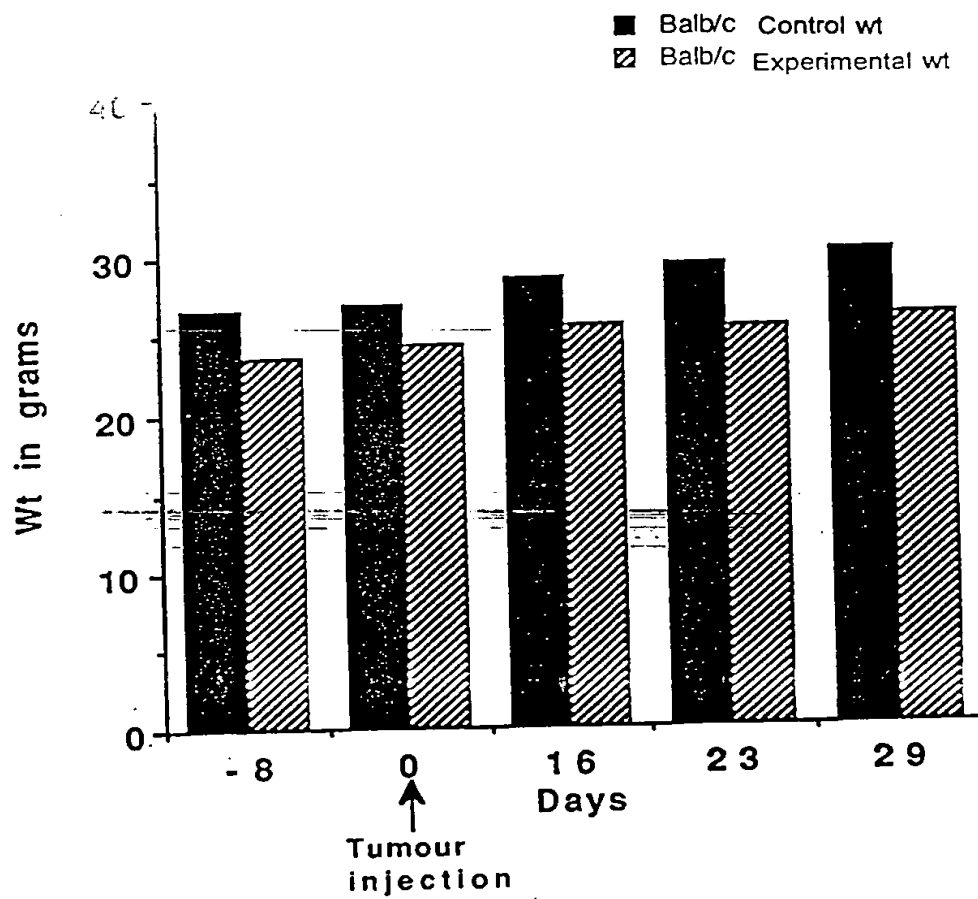


3/5

* Number of mice in group

THIS PAGE BLANK (USPTO)

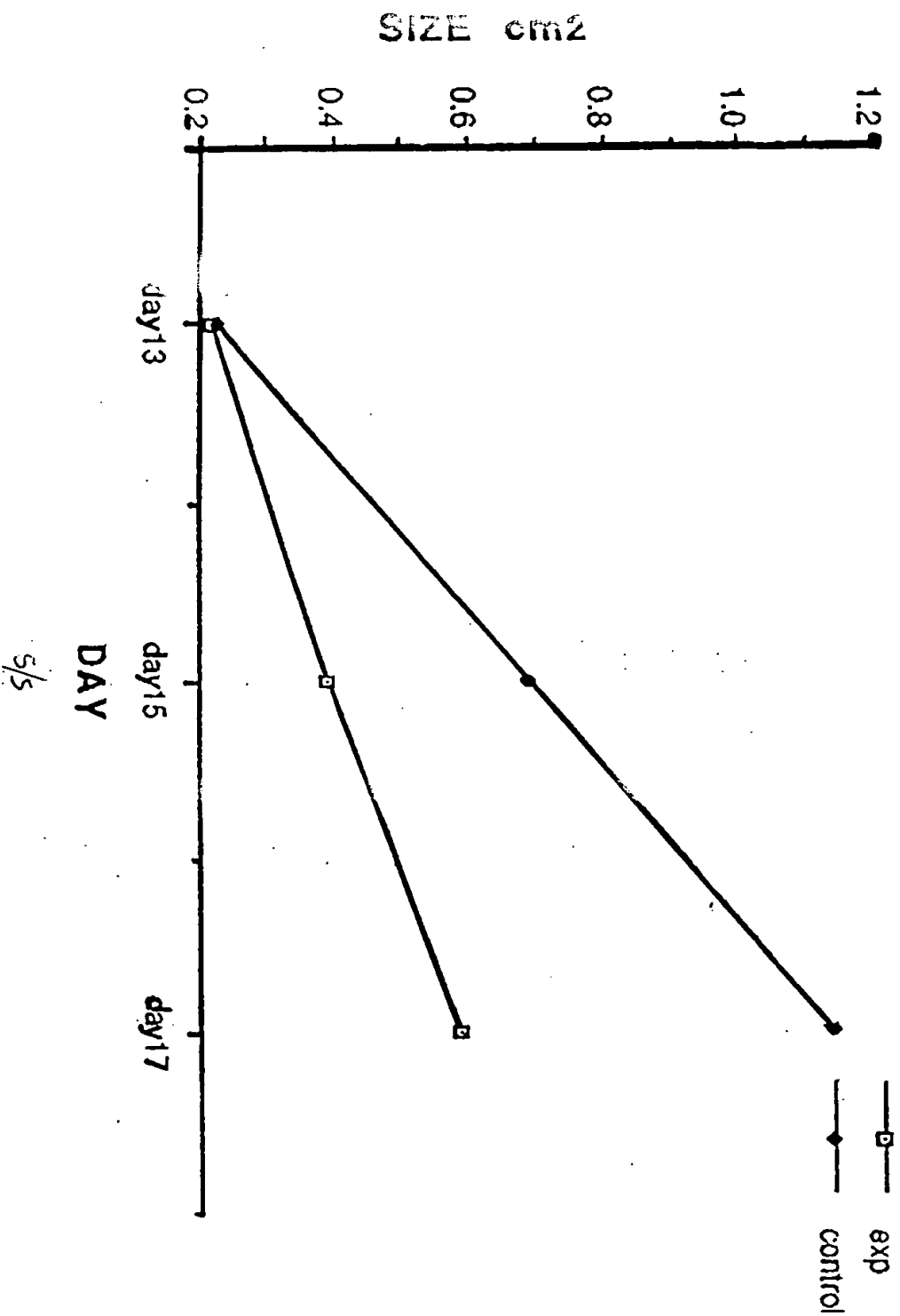
Figure 4. Weight of Balb/c mice



THIS PAGE BLANK (U&PTO)

Figure 5

Growth of tumours (means)



PCT NO. GB00/03770

Sarah Griffin.

THIS PAGE BLANK (USPTO)